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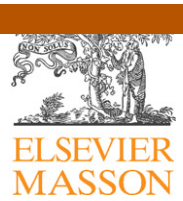

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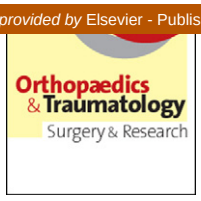

ORIGINAL ARTICLE

Does fibrin sealant use in total knee replacement reduce transfusion rates? A non-randomised comparative study

P. Massin*, C. Scemama, C. Jeanrot, P. Boyer

Department of Orthopaedic Surgery, Bichat Claude-Bernard Teaching Hospital Center, Paris Diderot University, 46, rue Henri-Huchard, 75877 Paris cedex 18, France

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KEYWORDS
Total knee replacement;
Blood loss;
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Summary
Background: Studies assessing fibrin sealants use during total knee replacement (TKR) have produced inconsistent results. We evaluated fibrin sealant therapy in TKR procedures performed without tourniquet and without postoperative drains.
Hypothesis: Use of a fibrin sealant during TKR decreases calculated total blood loss, thereby diminishing blood transfusion requirements and costs.
Patients and methods: We studied 62 patients with primary knee osteoarthritis who underwent TKR by the same surgeon between September 2009 and December 2010. Fibrin sealant was used only in the last 31 patients, who were compared to the first 31 patients regarding calculated total blood loss, blood transfusion rate, and mean number of red-blood-cell units used per patient. Costs were compared in the two groups.
Results: In the control group, mean total blood loss calculated using the method of Gross was 1.3 ± 0.6 L, 48% of patients required blood transfusions, and the mean number of units per patient was 0.9 ± 1. In the fibrin-sealant group, 29% of patients required blood transfusions and the mean number of units was 0.6 ± 0.9. The between-group differences in favour of the fibrin-sealant group were not statistically significant. In each group, compared with patients not requiring blood transfusions, patients needing transfusions had significantly lower starting preoperative haemoglobin values and a significantly greater positive difference between the calculated total blood loss and the maximum allowable blood loss. In the test group, the cost of the 31 units of fibrin sealant was 9743 € and the cost reduction due to using 11 fewer red-blood-cell units was only 3484 €. Hospital stay was not significantly shorter in any of the two groups.
Discussion: Blood transfusion minimisation during TKR should rely chiefly on correcting pre-operative anaemia and optimizing transfusion decisions based on the difference between the

* Corresponding author. Tel.: +33 1 40 24 75 03; fax: +33 1 40 25 71 84.
E-mail address: philippe.massin@bch.aphp.fr (P. Massin).

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total blood loss and the maximum allowable blood loss. Fibrin sealant did not significantly diminish transfusion requirements in our study. Randomised studies in larger patient populations are needed. The cost of fibrin sealant may exceed the expected cost savings in relation with decreased blood transfusion requirements.
Level of evidence: Level III (before-after therapeutic study).

Introduction

Blood loss minimisation during orthopaedic surgical procedures is a major concern given the limited availability of blood products and the risks associated with both blood transfusion and postoperative anaemia [1]. Strategies suggested to date include intra- and postoperative cell salvage, tranexamic acid therapy and autologous blood transfusion. However, there are numerous contraindications to tranexamic acid [2,3], and autologous blood transfusion is declining in popularity because of its cumbersome nature, particularly in elderly patients. Fibrin sealants were developed long ago and found effective in several orthopaedic procedures on the hip, knee, and spine [4—9].

Total knee replacement (TKR) is associated with significant blood loss. Thus, total blood loss (TBL) ranges from 1.2 to 1.8 L or more. Substantial bleeding occurs via the drains during the first few postoperative days [2,3,9—13], and 24 to 58% of patients require blood transfusions [8—10,14—16]. The application of fibrin sealant during TKR has been reported to decrease bloody drainage during the postoperative period [8,9], thereby diminishing the total amount of blood lost [9]. However, effects on the blood transfusion rate have varied across studies. Thus, the blood transfusion rate decrease seen with fibrin sealant was significant in a study by Levy et al. [9] but non-significant in a study by Wang et al. [8].

Here, we report a preliminary prospective non-randomised study in 62 consecutive patients undergoing TKR. Fibrin sealant was used only in the last 31 patients. To minimize postoperative blood loss, we made two changes to our usual surgical protocol at the beginning of the study: we performed step-by-step haemostasis instead of using a tourniquet, with the result that bleeding at the end of the procedure was sufficiently limited to obviate the need for drains. The study intervention consisted in spraying fibrin sealant over the entire surgical field in the last 31 patients. Our working hypothesis was that fibrin-sealant therapy would further decrease the calculated TBL, thereby diminishing blood transfusion requirements. We prospectively monitored and compared the control group and the test group in order to evaluate our working hypothesis. We also compared costs in the two groups.

Patients and methods

We included 62 patients who underwent unilateral TKR by the same surgeon (PM) at our institution between September 2009 and December 2010. The reason for TKR was advanced primary knee osteoarthritis in all patients. None of the patients had coagulation disorders.

The first 31 patients had surgery between September 2009 and February 2010, without fibrin sealant. In the last 31 patients, who had surgery between February and December 2010, a single change was made to the surgical protocol, namely the addition of a fibrin-sealant spray. Table 1 reports the main patient characteristics. No significant differences were found between the control and fibrin-sealant groups for age, sex, body mass index (BMI), or American Society of Anesthesiologists (ASA) score. The mean preoperative haemoglobin concentration was significantly higher in the fibrin-sealant group.

We used fibrin sealant derived only from human plasma (Quixil®, Ethicon, Johnson & Johnson, Depuy France, Issy-les-Moulineaux, France). This product replicates the final steps of the clotting cascade. Each 5 ml dose contains a concentrate of human clottable proteins, a solution of purified human thrombin, and calcium chloride.

The same surgical procedure was used in all 62 patients. The cementless prosthesis for primary TKR Natural Knee® II (Zimmer, Warsaw, IN, USA) was implanted via the subvastus medialis approach, without patellar resurfacing. Computer-assisted navigation was used in all patients, obviating the need for an intramedullary guidewire. No tourniquet was used, and step-by-step haemostatic electrocoagulation was performed. The Quixil® administration device was used to administer the 5 ml fibrin-sealant dose (Fig. 1). The thrombin and clottable-protein mix are packaged in two separate vials connected via two separate ports to a syringe that has a single plunger and nozzle, so that both solutions are drawn simultaneously and mixed in the syringe. We connected the syringe to a pressure regulator to achieve a uniform spray by depressing the plunger. The nozzle was held about 15 cm from the tissues, which were as dry as possible, to ensure coverage with a superficial film of fibrin sealant. Fibrin sealant was first applied to the posterior part of the joint before implantation of the prosthetic components. The remaining sealant was applied on the anterior aspect of the surgical field, after prosthesis implantation and just before wound closure. No drains were left in place. A compression bandage was used for the first 8 h.

Prophylactic low-molecular-weight heparin therapy was given for 1 month. Sitting was started on the first postoperative day and standing with weight bearing on the next day. A continuous passive motion machine was used starting on the first postoperative day, with a femoral nerve block achieved via a portable elastomeric pump loaded with ropivacaine solution. The femoral nerve block was replaced by subcutaneous opioid analgesics after 48 h and subsequently by step-1 analgesics based on the visual-analogue-scale pain score. Patients were discharged to rehabilitation centres 7 to 10 days after surgery depending on bed availability.

Table 1 Comparison of the demographic data and results in the groups with and without fibrin-sealant therapy (Quixil®).

	Without Quixil® $n=31$	With Quixil® $n=31$	*P* value	Power (%)
Age	72 ± 8	69 ± 10	< 0.2	
M/F ratio	0.29	0.55	< 0.2	
Blood volume in L	4.4 ± 0.8	4.6 ± 0.5	< 0.2	
Preoperative Hb in g/dL	13 ± 1.2	14 ± 1	< 0.04*	
ASA 1/2/3	11/16/4	12/18/1	< 0.3	
Blood loss in L (Gross)	1.34 ± 0.57	1.44 ± 0.63	< 0.3	10
Blood loss in L (Mercuriali)	0.60 ± 0.44	0.55 ± 0.38	< 0.8	7.70
Blood transfusion rate	0.48	0.29	< 0.1	33.30
Mean number of RBC units/patient	0.9 ± 1.1	0.6 ± 0.9	< 0.2	21.70

M: male; F: female; Hb: haemoglobin; ASA: American Society of Anesthesiologists; L: litre; dL: decilitre; RBC: red-blood-cell.
* Statistically significant difference.

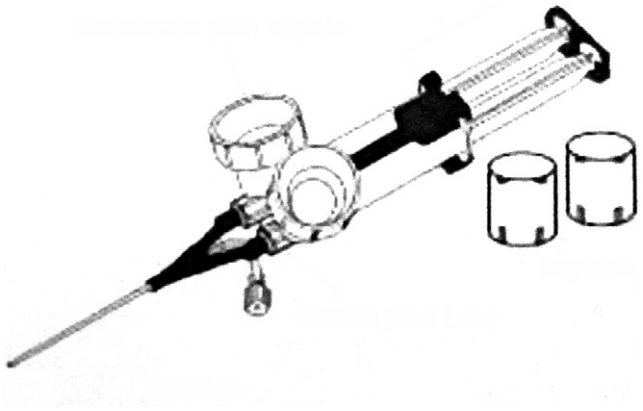

Figure 1 Ready-to-use kit for applying the fibrin sealant (Quixil®).

The study was conducted prospectively. A specific blood transfusion protocol was followed. No blood transfusions were given during surgery. Homologous blood transfusions were used as needed during the postoperative period, after the patients had returned to the surgical ward. The haemoglobin concentration was determined on the first and third postoperative days and at discharge. Prescribing recommendations were based on the 1988 National Institutes of Health consensus conference indicating 8 g/dL as the lowest acceptable haemoglobin concentration with a haematocrit no lower than 27% in women and 30% in men [17]. As shown in Table 2, the protocol was adjusted according to specific patient characteristics (age, cardiovascular history, ASA score, and clinical tolerance of the anaemia). Blood transfusions were given on the third and fourth postoperative days. The haemoglobin concentration was determined 2 days after the last blood transfusion.

The main evaluation criterion was calculated TBL. The secondary evaluation criteria were the blood transfusion rate and the mean number of red-blood-cell (RBC) units per patient. TBL was computed based on the haemoglobin concentration drop according to Gross [18] and on the Mercuriali and Inghilleri formula [19] taking into account both non-compensated blood loss and compensated blood loss, with each homologous RBC unit being considered equivalent

Gross	Mercuriali and Inghilerri
TBL= total blood volume* (Ht preop- Ht t)/ ((Ht preop+ Ht t)/2))	TBL = NCBL + CBL
TBL= Total Blood Loss Ht t : Lowest Postoperative Haematocrit	TBL= Total Blood Loss NCBL= Non Compensated Blood Loss ((Ht preop- Ht J6)*total blood volume) CBL= Compensated blood loss (150 mL* number of RBC units) Ht J6 : 6-day postoperative Haematocrit

Figure 2 Formulas of Gross and of Mercuriali and Inghilerri for estimating total blood loss.

to 150 mL of blood volume (Fig. 2). These two methods produce noticeably different results, since the method described by Gross uses the mean of the preoperative and of the lowest postoperative haematocrit values. With both methods, the haemoglobin drop is weighted for blood volume estimated using Nadler's formula [20]. As no drains were used, postoperative exteriorized bleeding was not measured. However, postoperative or apparent bleeding was shown an unreliable parameter because it does not reflect the real calculated blood loss [21,22].

To identify factors associated with the blood transfusion rate, we evaluated the influence in each group of age, ASA score, preoperative haemoglobin concentration, TBL,

Table 2 Blood transfusion protocol used in both study groups.

Haemoglobin level	
7 to 9 g/dL	Transfusion except if Age < 60 years AND ASA 1 AND good clinical tolerance Age > 75 years
9 to 10 g/dL	No transfusion except if AND/OR history of cardiovascular disease AND/OR ASA 2 or 3 AND/OR poor clinical tolerance

ASA: American Society of Anesthesiologists.

and the difference between the maximum allowable blood loss (MABL) and the TBL according to Helm et al. [15] (in theory, a negative difference indicates a need for blood transfusion). We retrospectively assessed compliance with the blood transfusion protocol by determining the number of patients transfused despite a positive MABL/TBL difference and the number not transfused despite a negative MABL/TBL difference in each group.

The cost of fibrin-sealant therapy was computed as the difference between the cost of the fibrin sealant used and the cost savings related to the blood-transfusion-sparing effect of fibrin-sealant therapy. Blood transfusion costs include the time spent by nurses to check compatibility and to administer the transfusion and the cost of storing and transporting the RBC units (546.12 British pounds for two units in a 2006 study by Agrawal et al. [23], i.e., 316 € per unit at the current exchange rate). At present, a 5 ml Quixil® dose costs 314.32 €. Costs may also be influenced by other factors such as a possible decrease in hospital stay length related to a blood transfusion-sparing effect of fibrin-sealant therapy. In our study, mean hospital stay length was 10 ± 2 days in the transfused group and 9 ± 3 days in the non-transfused (NS) group. However, we did not specifically study this parameter, as it was biased by discharge delays due to limited bed availability in rehabilitation centres.

For the statistical analysis, we used Student's *t* test to compare quantitative variables (e.g., TBL, age and BMI), or the Mann-Whitney test for groups of fewer than 25 patients; and the chi^2 test for qualitative variables and proportions (e.g., blood transfusion rate, sex distribution, and ASA score distribution), with Yates' correction for small sample sizes if appropriate. Values of *P* smaller than 0.05 were considered significant. Statistical power for detecting differences in TBL values and transfusion rates was assessed based on sample size and standard deviations.

Results

In the control group (no fibrin sealant), calculated TBL was 0.60 ± 0.43 L, according to Mercuriali and Inghilleri and 1.34 ± 0.57 L, according to Gross. The transfusion rate was 48% and the mean number of units per patient was 0.9 ± 1 (Table 1 and Fig. 3).

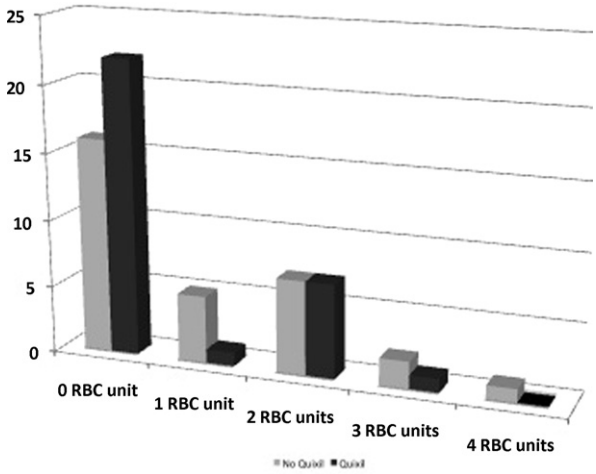

Figure 3 Distribution of the number of red-blood-cell (RBC) units in the groups with and without fibrin-sealant therapy. Fibrin-sealant therapy was associated with the use of 11 fewer RBC units.

Calculated TBL obtained using the method of Gross or that of Mercuriali and Inghilleri was not significantly different in the fibrin-sealant group compared to the control group. The fibrin-sealant group had a lower transfusion rate (29% versus 48%) and a smaller number of units per patient (0.6 ± 0.9 versus 0.9 ± 1.1) but neither difference was statistically significant (Table 1). No blood transfusion-related complications were recorded. The only adverse event was sterile wound discharge requiring wound revision in one patient in the fibrin-sealant group.

Within-group comparisons of transfused and NS patients showed no significant differences for age, ASA score, estimated blood volume, or TBL. In contrast, highly significant differences were found for preoperative haemoglobin concentration and the MABL/TBL difference (Tables 3 and 4). We retrospectively identified 10 deviations to our protocol. In six patients (three in each group), our protocol indicated a need for blood transfusion based on a haemoglobin level between 9 and 10 g/dL with age older than 75 years and an ASA score of 2 or 3, but these patients were not transfused. In five of these six patients, TBL was larger than MABL. In four patients (two in each group), blood transfusion was

Table 3 Comparison of transfused and non-transfused patients within the group given fibrin-sealant therapy (Quixil®).

	Transfusion $n = 9$	No transfusion $n = 22$	*P* value
Age	73 ± 7	67 ± 11	< 0.3
M/F ratio	0.50	0.57	< 0.5
Blood volume (l)	4.5 ± 0.4	4.6 ± 0.6	< 0.42
ASA 1/2/3	2/7/0	10/11/1	< 0.1
Preoperative Hb in g/dL	12.7 ± 1.0	14.1 ± 1.2	< 0.01*
TBL in L (Gross)	1.7 ± 0.8	1.3 ± 0.5	< 0.13
TBL- MABL (mL)	479 ± 776	-158 ± 492	< 0.02*

M: male; F: female; Hb: haemoglobin; ASA: American Society of Anesthesiologists; Hb: haemoglobin concentration; L: litre; mL: millilitre; TBL: total blood loss; MABL: maximum allowable blood loss.
* Statistically significant difference.

Table 4 Comparison of transfused and non-transfused patients within the group not given fibrin-sealant therapy.

	Transfusion $n = 15$	No transfusion $n = 16$	p value
Age	75 ± 9	71 ± 8	< 0.12
M/F ratio	0.15	0.45	< 0.3
Blood volume (l)	4.2 ± 0.7	4.6 ± 0.8	< 0.22
ASA 1/2/3	4/8/03	7/8/01	< 0.3
Preoperative Hb in g/dL	12.3 ± 1.2	13.7 ± 0.8	< 0.005*
TBL in L (Gross)	1.3 ± 0.6	1.3 ± 0.6	< 0.82
TBL-MABL (mL)	327 ± 398	-129 ± 505	< 0.002*

M: male; F: female; Hb: haemoglobin; ASA: American Society of Anesthesiologists; Hb: haemoglobin concentration; L: litre; mL: millilitre; TBL: total blood loss; MABL: maximum allowable blood loss.
* Statistically significant difference.

ordered despite haemoglobin concentrations greater than 10 g/dL because of a history of severe cardiovascular disease. In three of these four patients, TBL remained smaller than MABL.

The cost of the 31 doses of fibrin sealant was 9743 €, which was more than the cost savings of 3484 € related to the use of 11 fewer RBC units.

Discussion

Using a fibrin sealant did not significantly decrease blood loss in our study. In contrast, Levy et al. [9] found a significant decline in calculated TBL from 1.7 to 1 L in a population similar to ours. A tourniquet and postoperative drains were used in the studies by Levy et al. [9] and Wang et al. [8]. Both studies showed a decrease in bloody drainage, which may therefore constitute the main effect of fibrin-sealant therapy.

Our fibrin-sealant group had a lower blood transfusion rate and a smaller mean number of RBC units per patient compared to the control group, but neither difference was statistically significant. In a population of similar size, Levy et al. found a significant drop in the transfusion rate from 55 to 20% in the fibrin-sealant group [9]. However, they did not report preoperative haemoglobin values, which may have introduced a substantial bias. Wang et al. [8] reported a non-significant decrease in the transfusion rate from 50% without Quixil® to 36% with Quixil® in groups of respectively 25 and 28 patients, which is consistent with our results but seems to contradict the significant decrease in bleeding in the earlier study [8]. However, when we compared transfused and NS patients, we found that the most powerful predictor of blood transfusion was the preoperative haemoglobin concentration and not TBL, in keeping with results by Cushner et al. [24]. The importance of the preoperative haemoglobin concentration is further supported by two studies [1,22] in which this parameter strongly predicted the risk of postoperative complications in patients with a history of cardiovascular disease. Therefore, the correction of preoperative anaemia deserves careful attention. Furthermore, we found that the difference between MABL and TBL was strongly associated with the risk of requiring blood transfusion, in agreement with a study by Helm et al. [15]. We identified ten deviations from our blood-transfusion protocol: six patients were not transfused despite meeting blood-transfusion criteria and four were transfused despite not meeting blood-transfusion criteria. As the frequency of protocol deviations was similar in the two groups, these deviations probably had no impact on the between-group comparisons. However, taking the difference between MABL and TBL into account would have decreased the number of deviant indications to one in each group.

Our cost analysis indicated that, in our hands, fibrin-sealant therapy increased the total cost of TKR. A blood transfusion rate decrease of 22% would have been statistically significant and would have spared the use of 16 RBC units, thereby decreasing costs by 4000 €, which would have been less than half the cost of the fibrin sealant (9743 €). Wang et al. [8] reported that using 25 Quixil® doses (7858 €) spared 13 RBC units (4108 €) and Levy et al. [9] that using at least 29 Quixil® doses (9115.28 €) spared 19 RBC units (6004 €). In the study by Levy et al. [9], in some cases two 5 mL kits were required per patient, which increased the cost. An analysis of these two studies [8,9] done by Steuten et al. [25] showed that using 5 mL Quixil® doses induced cost savings when absence of blood transfusions was associated with shorter hospital stays, which was not the case in our study.

Our study has several limitations. We used a non-randomised design. However, performance bias was minimised, as all procedures were done by the same surgeon, a noticeable difference with the two randomised studies of fibrin-sealant therapy in TKR. Second, the statistical power of the comparison was diminished by the marked variability in blood loss, to only 10% (i.e., there was a 90% risk of finding no difference although a difference exists). To obtain 50% power, 300 patients would have been required in each group. Power was 33% for finding a significant difference in the blood transfusion rate. Finally, the higher preoperative haemoglobin concentration in the Quixil® group would have been expected to decrease the blood transfusion rate in this group. However, despite this source of bias in favour of the test group, no significant difference in the blood transfusion rate was found between the two groups.

In conclusion, blood loss minimisation is challenging regardless of the surgical technique used. Conceivably, studies in larger populations of patients having similar

preoperative haemoglobin concentrations might find evidence that fibrin sealants are effective. However, blood loss minimisation during TKR should rely chiefly on correction of preoperative anaemia and on the use of blood transfusion protocols with adjustments not only for age and the ASA score, but also for MABL. The present cost of fibrin sealants seems to preclude a cost-saving effect related to decreased use of blood products.

Disclosure of interest

PM has been an invited speaker for Ethicon S.A.S.

CS, CJ, PB declare that they have no conflicts of interest concerning this article.

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